

THE PRESENT AND FUTURE

JACC REVIEW TOPIC OF THE WEEK

Lymphatic Dysregulation in Patients With Heart Failure

JACC Review Topic of the Week



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ABSTRACT

The lymphatic system is an integral part of the circulatory system and plays an important role in the volume homeostasis of the human body. The complex anatomy and physiology paired with a lack of simple diagnostic tools to study the lymphatic system have led to an underappreciation of the contribution of the lymphatic system to acute and chronic heart failure (HF). Herein, we discuss the physiological role of the lymphatic system in volume management and the evidence demonstrating the dysregulation of the lymphatic system in HF. Further, we discuss the opportunity to target the lymphatic system in the management of HF and different potential approaches to accessing the lymphatic system. (J Am Coll Cardiol 2021;78:66–76) © 2021 by the American College of Cardiology Foundation.

The circulatory system consists of the cardiovascular system and the lymphatic system. The cardiovascular system is a closed, high-pressure circulatory system with the heart acting as a central pump, whereas the lymphatic system is an open, low-pressure circulatory system with no central pump (1). The lymphatic vessels are present in almost all tissues except bone marrow, cartilage, and cornea (1). Several liters of fluids are filtered via the semipermeable membrane of the capillaries into the interstitial space every day. The filtered fluid has important physiological functions, such as tissue nutrition and hydration. An increase in the amount of the filtered fluid can

lead to interstitial edema with clinical manifestations such as extremity and tissue edema, including pulmonary edema. The amount of filtered fluids depends on the Starling equation for fluid filtration (2):

$$J_v = L_p S [(p_c - p_i) - \sigma(\pi_c - \pi_i)]$$

where J_v is the filtration volume per second, L_p is the hydraulic conductance of the membrane, S is surface area for filtration, p_c is the capillary hydrostatic pressure, p_i is the interstitial hydrostatic pressure, σ is the reflection coefficient, π_c is the oncotic pressure of the plasma protein, and π_i is the oncotic pressure of the interstitial protein (Figure 1).



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HIGHLIGHTS

- The lymphatic system is integral to volume hemostasis.
- The lymphatic system is involved in many of the clinical manifestations of HF.
- In patients with HF, therapeutic targeting of the lymphatic system could reduce congestive symptoms.

One of the main functions of the lymphatic vascular system is to collect filtered fluid that accumulates in the interstitial space (mainly water, salts, and plasma proteins) and return it to the central venous system. To prevent interstitial edema, the return of filtered lymph fluid occurs at a rate similar to the rate of fluid production/accumulation in the interstitial space (2). After fluid enters the lymphatic vascular system, it becomes lymph and passes through lymph nodes, where foreign matter is filtered and neutralized by the immune system cells (eg, dendritic cells, macrophages, and lymphocytes) (2).

Although lymph composition was thought to be similar to that of the plasma, proteomic mapping has shown unique composition of the tissue-derived proteins in the lymph (3). Lymph contains high concentrations of proteins that are involved in cell catabolism and apoptosis, extracellular matrix

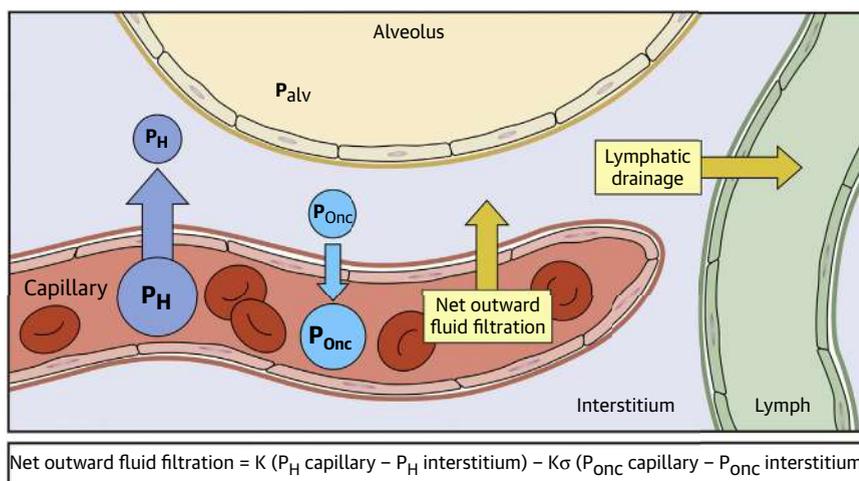
remodeling, and innate immunity (3). Besides its role in fluid hemostasis, lymph acts as a chemical buffer system, facilitates immune cell trafficking, and transports proteomes to draining lymph nodes (3).

Lymph is returned to the cardiovascular system through 2 major lymphatic ducts that empty into the venous system (ie, the right lymphatic duct and the thoracic duct) (4). The right lymphatic duct drains lymph from the right side of thorax, right upper extremity, and right side of head and neck, and empties into the junction of the right internal jugular vein and right subclavian vein (Figure 2) (4). The thoracic duct runs superiorly from the superior aspect of the cisterna chyli to the lower cervical spine, drains lymph from all the body except parts that are drained by the right lymphatic duct, and empties into the junction of the left internal jugular vein and the left subclavian vein (5). The thoracic duct terminates as a single duct in the majority of cases (72%), or less frequently as double (8.5%), triple (1.8%), or quadruple (2.2%) ducts (6). The thoracic duct typically returns approximately 1.38 mL/kg/h of lymph to the central venous circulation (5). An increase in the filtration volume (arterial/venous congestion) is counteracted with an increase in the amount of filtered lymph fluid and a decrease in interstitial protein, thus decreasing the oncotic pressure of the interstitium (7).

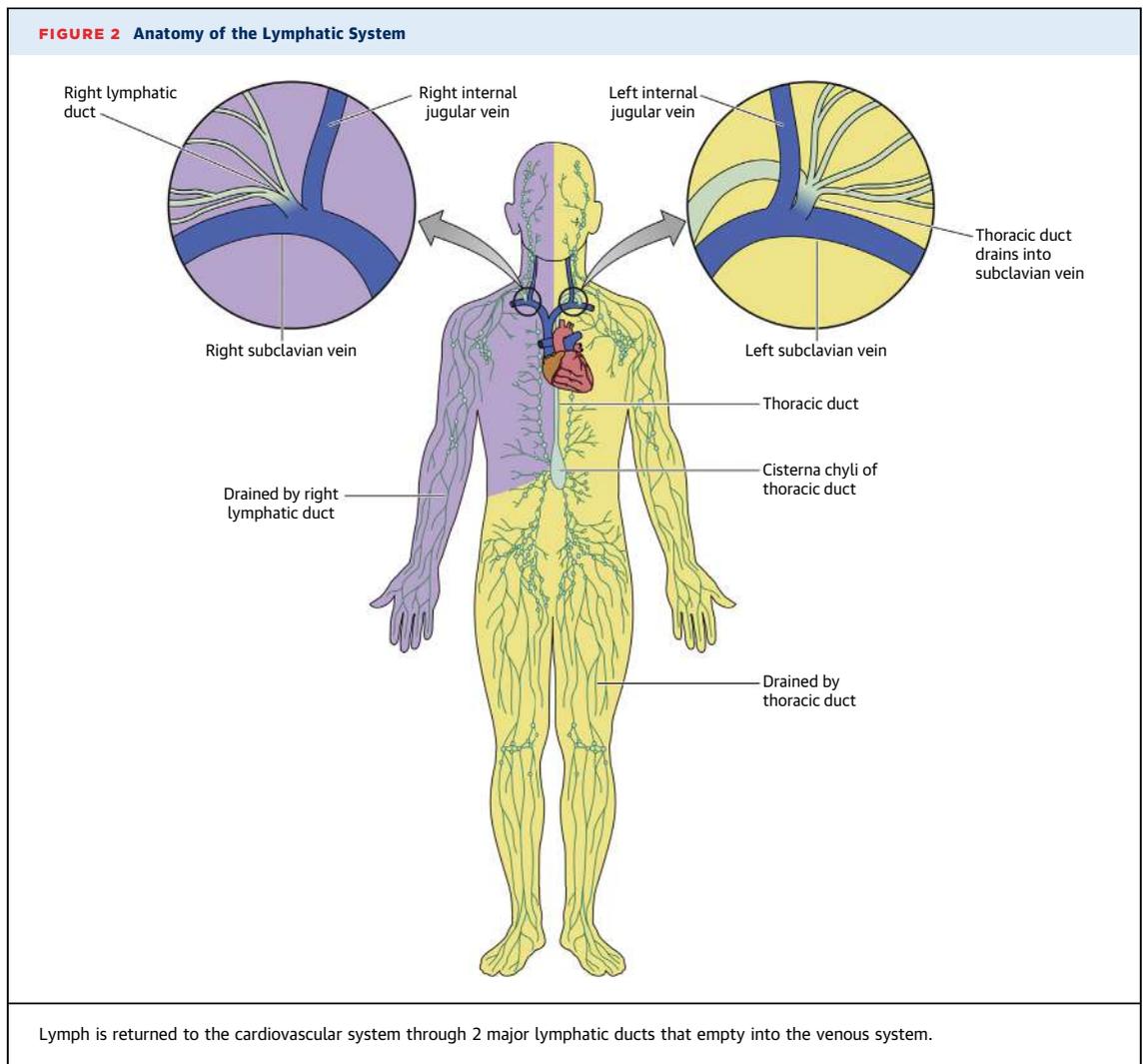
ABBREVIATIONS AND ACRONYMS

- CRS** = cardiorenal syndrome
- CVP** = central venous pressure
- HF** = heart failure
- PCWP** = pulmonary capillary wedge pressure
- SMC** = smooth muscle cells

FIGURE 1 Basic Principles of Fluid Shifts Between Individual Compartments and Lymph Production



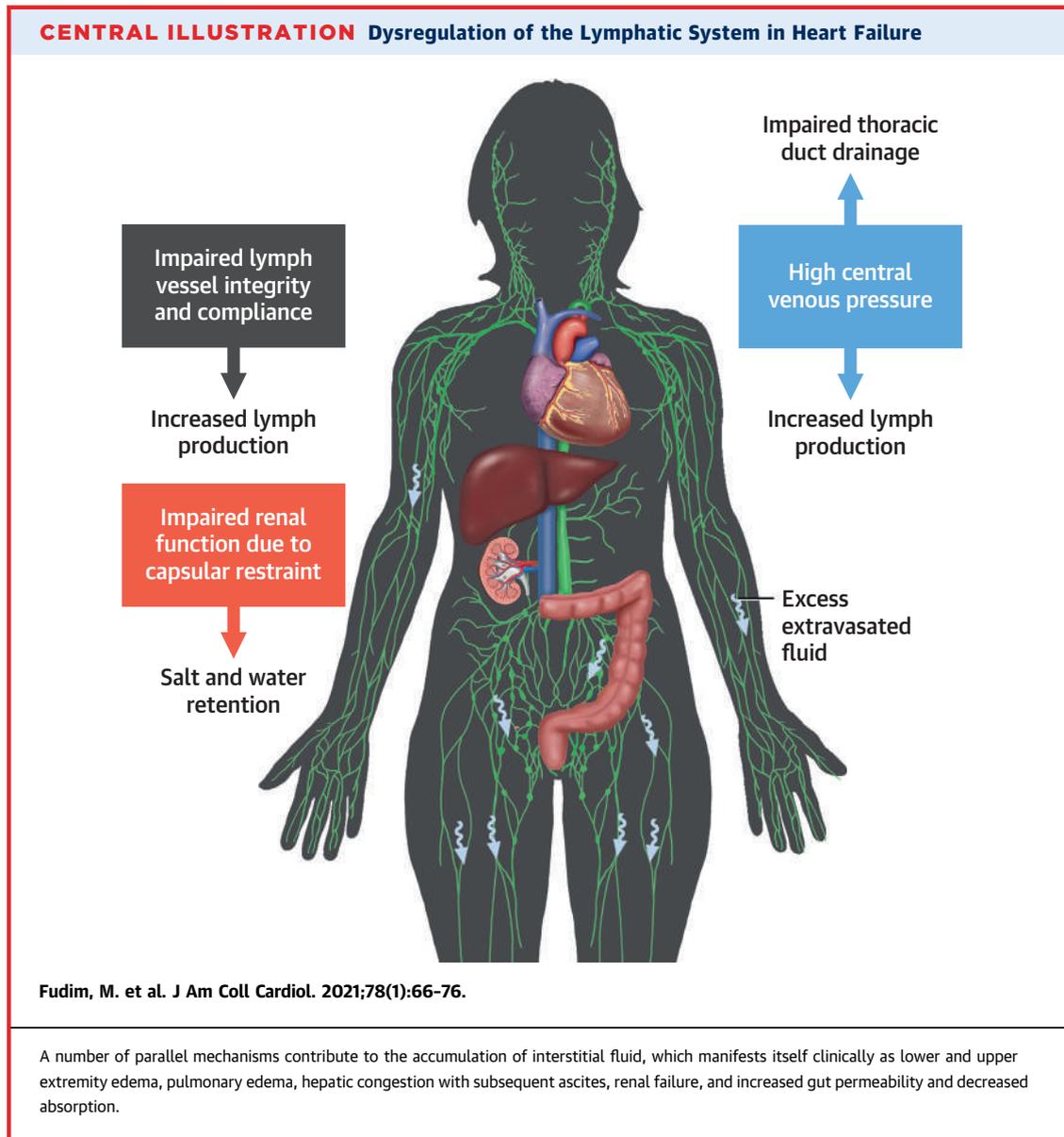
The amount of filtered fluids depends on the Starling equation. Fluid extravasation depends on the balance of hydrostatic pressure, and oncotic pressure in the capillaries and the interstitium. K = constant; P_{alv} = alveolar pressure; P_H = hydrostatic pressure; P_{Onc} = oncotic pressure.



Lymphatic vasculature consists of capillaries, pre-collectors, and collecting lymphatic vessels. Microscopically, lymphatic vasculature is distinct from that of blood vasculature (8). For example, blood capillaries are lined with blood vascular endothelial cells, which are supported by basement membranes, and covered by smooth muscle-like pericytes, whereas lymphatic capillaries are composed of a single layer of partly overlapping lymphatic endothelial cells with no basement membrane or pericytes (8). Pre-collectors are covered by scant smooth muscle cells (SMCs) and drain into the collecting lymphatic vessels, which are more extensively covered by SMCs (9). Within the lymphatic vasculature, there are molecular differences in the profiles of contractile proteins of SMCs (10). For example, mesenteric lymphatics display all 4 actin types (ie, cardiac, vascular, enteric, and skeletal α -actins), whereas the thoracic duct predominantly displays cardiac and vascular α -actins (10).

DYSREGULATION OF THE LYMPHATIC SYSTEM IN HEART FAILURE

The lymphatic system is commonly ignored when considering the pathophysiology of heart failure (HF) (11), yet its contributions to the observed clinical manifestations of HF are important (11). HF is marked by venous congestion (12). Increased central venous pressure (CVP) is a major determinant of adverse clinical outcomes (eg, impaired renal function) and is an independent predictor of mortality in patients with HF (13). Additionally, most HF hospitalizations are related to manifestations of venous congestion rather than low cardiac output (14). Vascular endothelial cells sense biomechanical forces and increased hydrostatic pressure resulting in a switch from a quiescent state to an activated state, which is marked by inflammation, vasoconstriction, and an increase in oxidative stress (15). Therefore, a chronic state of



venous congestion can lead to organ damage, such as pulmonary vascular remodeling, hepatic injury, and renal injury.

MECHANISMS OF LYMPHATIC CONGESTION IN HF

Similar to venous congestion, lymphatic congestion is a hallmark of HF and drives both symptom manifestation and adverse outcomes in this population. In HF, a number of parallel mechanisms contribute to the accumulation of interstitial fluid, which manifests itself clinically as lower and upper extremity edema, pulmonary edema, hepatic congestion with subsequent ascites, renal failure, and increased gut

permeability and decreased absorption (16) (**Central Illustration**).

1. Increased filtration. Higher capillary hydrostatic pressure (aka, venous congestion in the tissue) results in increased fluid filtration, and thus, greater extravasation of fluid in the interstitial space. In the absence of an equivalent increase in lymph fluid clearance from the tissue, there is both acute and chronic extravascular fluid accumulation.
2. Decreased drainage. An increase in CVP prevents the emptying of lymph via the thoracic duct into the central venous circulation. Central venous lymph drainage is a passive process and depends

on a negative pressure gradient from tissue → thoracic duct → central veins.

3. Impaired lymph vessel integrity and compliance. Increased vascular permeability (aka, vascular leakage) enhances the extravasation of plasma and protein with resultant accumulation of interstitial fluid. HF is characterized by a systemic pro-inflammatory state (17). Systemic inflammation, irrespective of the underlying etiology (eg, sepsis, HF, cancer) increases vascular permeability caused by disintegration of the vascular barrier; thus, large molecules, such as proteins, can leak into the interstitial space (18). This subsequently decreases the oncotic pressure of plasma and increases the interstitial oncotic pressure, with a net increase in filtration volume. In response to the increase in interstitial fluid accumulation and the need to increase lymph flow, lymphatics adapt via a change in contractile activity (19). Although this adaptation seems to be effective in acute inflammation, lymph transport decreases significantly in chronic inflammation (eg, in HF), which may signify impaired lymph vessel integrity and compliance in these states (19). Further, infiltrating neutrophils during inflammation release neutrophil elastase that degrades elastin microfibril interfacier 1, thus weakening the intercellular junctions of lymphatic endothelial cells with subsequent lymphatic vessel collapse (20). Additionally, in certain conditions, such as radiation-induced heart disease, impaired lymph vessel integrity can contribute to some of the manifestations of HF (21); radiation can decrease lymphangiogenesis resulting in extravascular volume accumulation (eg, pericardial effusion) (21).
4. Dysfunctional lymphatic and lymphovenous valves. Lymphatic vessels contain lymphatic valves, which regulate a unidirectional lymph flow. Dysfunction of the lymphatic valves can lead to lymph reflux and lymphedema (22). Additionally, lymphovenous valves regulate the return of lymph to the cardiovascular system (22), although the role of lymphatic and lymphovenous valves in HF has not been studied. The chronic increase in central venous pressure (as seen in HF) may lead to dysfunctional lymphatic and lymphovenous valves caused by a retrograde increase in the lymphatic pressure.
5. Dysregulated renal lymphodynamics. Elevated inferior vena cava pressure in HF with subsequent elevation in renal vein pressure results in an increase in renal lymph flow and sodium content and a decrease in urinary sodium content (23). Further, increased renal lymph flow accelerates washing

out interstitial proteins with subsequent decrease in the renal interstitial colloid osmotic pressure, thus promoting passive sodium reabsorption (23). These changes result in increased sodium and fluid retention in HF.

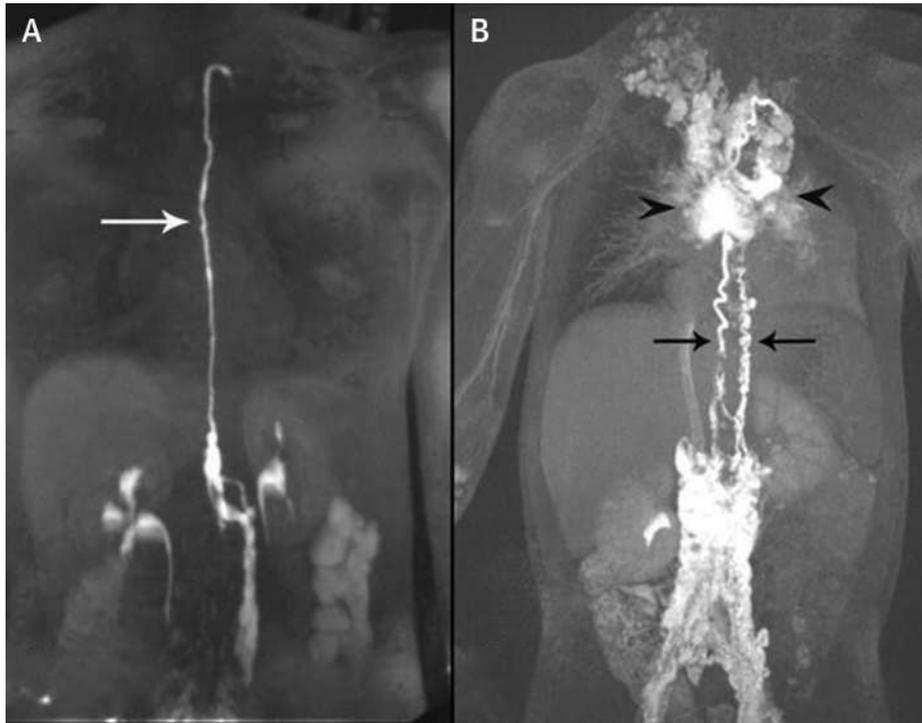
6. Maladaptive lymphangiogenesis resulting in myocardial remodeling. There is a growing body of evidence suggesting an important role for the lymphatic system in counteracting myocardial edema and inflammation in various ischemic and nonischemic heart disease conditions. Insufficient lymphangiogenesis (eg, after myocardial infarction) can lead to myocardial interstitial fibrosis, cardiac remodeling, and cardiac dysfunction (24).

Individually, these components are unlikely to lead to accumulation of interstitial fluid, given that compensatory mechanisms allow for regulation of lymph flow across a broad range of perturbations. Yet, in HF, the previously listed derangements likely occur in parallel, overwhelming the homeostasis of lymph production and drainage.

Lymphatic dysfunction and remodeling have repeatedly been demonstrated in HF-related comorbidities, such as type 2 diabetes mellitus (25), hypertension (26), and obesity (27), and with increased age (28). Diet-induced obesity animal models are associated with reduced lymphatic capillary density and reduced dermal lymphatic collecting vessel pumping rates. Further, increased immune cell accumulation surrounding lymphatic vessels and impaired vessel dilatation (reduced local nitric oxide production) have been described. Decreased lymphangiogenesis and impaired vessel integrity have been described in animal models of diabetes mellitus (29). Notably, impaired lymph drainage can also directly affect the heart, leading to chronic myocardial edema, inflammation, and fibrosis with resultant cardiac dysfunction, as shown in animal models of myocardial infarction (30).

Evidence for an impaired lymphatic system in humans with HF is limited. Houston et al. (31) showed that the level of the lymphangiogenic factor *vascular endothelial growth factor-D* is positively correlated with the left heart filling pressures and duration of HF diagnosis. This finding might suggest a compensatory mechanism to augment lymphatic clearance of the congested pulmonary tissue. Recent evidence suggests that in patients with HF and preserved ejection fraction, the number of lymphatic vessels is decreased, but diameters are increased (likely caused by elevated backward pressure from the central venous system) (32). Impaired lymphatic vessel compliance likely contributes to a reduced filtration

FIGURE 3 Magnetic Resonance Lymphangiography of the Central Lymphatic System



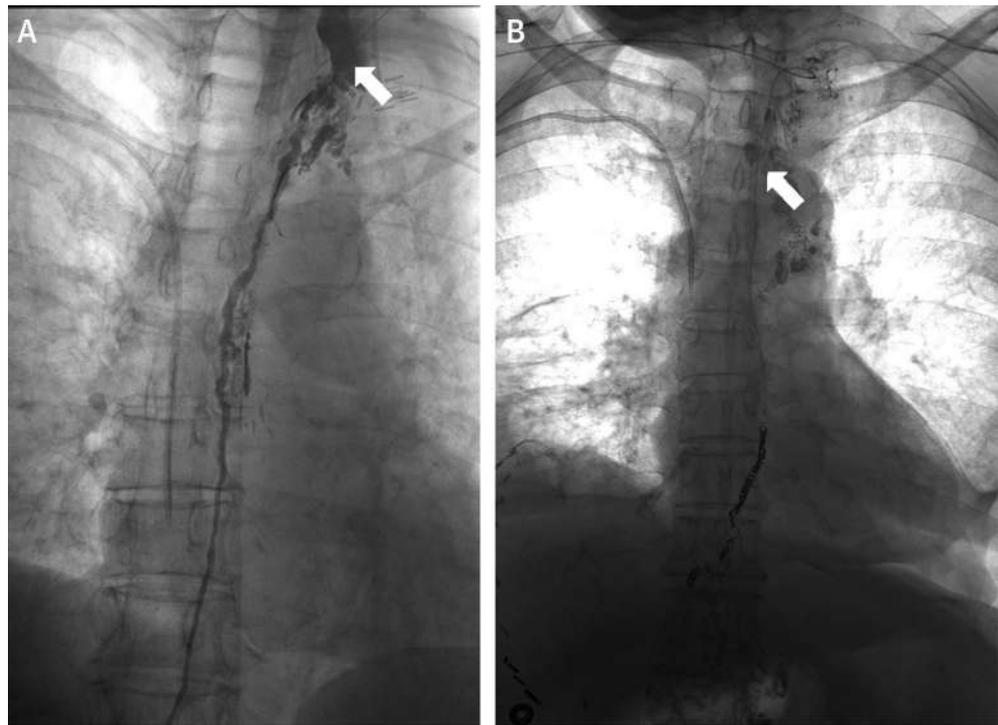
(A) Normal single thoracic duct (white arrow). (B) Bilateral thoracic ducts (black arrows) and abnormal pulmonary lymphatic flow from thoracic ducts toward lung parenchyma (black arrowheads). Reproduced from Itkin et al. (61).

coefficient and thus tissue clearance of extravasated fluid (32).

As fluid builds in the interstitial space, more fluid would be expected to be drained by the lymphatic system. In the setting of normal plasma oncotic pressure, a gradual increase in capillary hydrostatic pressure is typically compensated by an increase in lymph flow (7). After a certain capillary hydrostatic pressure threshold is reached, the lymphatic vascular system fails to compensate for any further increase in hydrostatic pressure or increase in filtration volume within the interstitial space.

In the lungs, for example, an acute increase in capillary hydrostatic pressure to a value >25 mm Hg results in pulmonary edema and decreased lung compliance (7). When hydrostatic pressure is chronically elevated, lymph flow may increase up to 30 times the normal rate (7,33). This may, in part, explain the absence of pulmonary edema in patients with HF who have chronically elevated pulmonary capillary wedge pressure (PCWP) as opposed to patients with acute elevation in PCWP (eg, in acute

mitral regurgitation) who tend to develop pulmonary edema even with a small increase in PCWP (33). Although there is no direct evidence that overwhelming of the lymphatic system is the driver of pulmonary edema formation in acute HF, several studies showed an important role of the lymphatic system in the management of pressure changes associated with HF. One of the early studies that examined this concept was in a dog model (34), showing that an acute rise in left atrial pressure is associated with an increase in right duct lymph flow. The same observation applies to right-sided HF; in an experiment (35) studying cor pulmonale in dogs, an increase in systemic venous pressure resulted in greater formation of capillary filtrate, accumulation of fluids in the lymphatic reservoir, and increase in thoracic duct lymph flow. Szabo et al. (36) showed that thoracic duct pressure increased in parallel to jugular vein pressure in dogs. This increase in thoracic duct pressure was associated with an increase in regional lymphatic pressure and abdominal lymphatic pressure.

FIGURE 4 Thoracic Duct Imaging and Cannulation

(A) Fluoroscopic image demonstrating opacification of the thoracic duct with a post-operative left cervical lymph leakage (white arrow) is shown. (B) The microcatheter is advanced down to the thoracic duct. Embolization coils were deployed by this retrograde access to stop the leakage.

The significance of passive lymph flow impairment leading to lymphatic congestion has been demonstrated in animals and humans. In an experimental sheep model (37), an increase in left atrial pressure and systemic venous pressure resulted in reduced lymph flow in the efferent duct of the caudal mediastinal lymph nodes and increase in pulmonary congestion. In an invasive hemodynamic study in patients with HF and preserved ejection fraction (38), patients who developed lung congestion during exercise had a similar increase in pulmonary blood flow as those who did not develop lung congestion. However, patients who developed lung congestion had higher pulmonary capillary wedge pressures and higher CVP than those who did not (38). This suggests that the development of lung congestion in these patients was largely driven by impaired lymphatic drainage of the lungs caused by elevated CVP. Finally, evidence of interstitial myocardial edema in patients with HF is directly linked to venous congestion, and resolution of interstitial myocardial edema follows cardiac decongestion (39).

THE LYMPHATIC SYSTEM IN HF: CARDIORENAL SYNDROME

Cardiorenal syndrome (CRS) is a clinical syndrome in which dysregulation of the heart and/or the kidneys leads to acute or chronic dysfunction of the other organ (40). The pathophysiology of CRS is poorly understood. The most common accepted explanation for the classical type 1 CRS is renal hypoperfusion with subsequent renin-angiotensin-aldosterone system and sympathetic nervous system activation and increase in arginine vasopressin secretion (40). However, this concept may only partially explain the CRS, as arterial hypotension is uncommon in the setting of acute HF (41), which would likely suggest a low likelihood of renal hypoperfusion. Venous congestion appears to be a far greater contributor to the pathophysiology of CRS. In patients with cardiac dysfunction secondary to pulmonary hypertension, Damman et al. (42) showed that CVP and renal blood flow were independent determinants of glomerular filtration rate. In patients admitted with

decompensated HF, Mullens et al. (43) showed that worsening renal function was associated with greater CVP.

Similar to the discussion of the lymphatic system for tissue congestion in HF, lymph accumulation also occurs in the kidneys. Renal lymphatic inflow may be overwhelmed in the setting of raised venous pressure (ie, venous congestion in HF) or augmented capillary permeability (eg, systemic inflammation). Finally, renal lymphatic outflow into the central venous system may be impaired caused by the increase in the CVP, acting as a functional outflow barrier to the highly congested thoracic duct (23). The result is renal interstitial edema (12). What makes the kidney unique is its capsule that limits organ stretch, thus increasing intrarenal pressure and ultimately causing renal dysfunction. Renal venous congestion decreases urinary flow and urinary sodium concentration, which is not merely a reflection of a reduced gradient across the kidney, but rather is a consequence of increased renal pressure (44). Increased venous pressure raises lymph production and clearance from the renal interstitium up to 4-fold. However, lymph flow reaches a plateau (around ~21 mm Hg) beyond which even decreasing outflow pressure does not change lymph flow (45).

CLINICAL EVALUATION OF THE LYMPHATIC SYSTEM

LYMPHATIC IMAGING. Part of the reason why the lymphatic system is not at the forefront when we think of HF, vascular congestion, and volume management is the inherent complexity in visualizing it. The lymphatic system was not visualized until 1952, when Kinmonth described pedal lymphangiography as a method of outlining the lymphatic system (46). Key features of the lymphatic system in HF are an increase in size of the thoracic duct and lymph nodes (47) and an increase in the lymph flow rate (48,49). Several imaging modalities exist today to evaluate the central lymphatic system. Although none of these imaging modalities are clinically used in HF, they can potentially aid in the assessment of HF severity and stratify patients who might benefit from lymphatic intervention.

Pedal lymphangiography involves cannulization of lymphatic ducts through small incisions on the dorsum of the feet using 30-gauge needles (50). Ethiodized oil (radiopaque) is injected through these needles followed by normal saline using a special pump; this eventually results in opacification of the cisterna chyli and thoracic duct (50). Intranodal lymphangiography is another technique that involves access of the

| TABLE Future Directions and Key Unanswered Questions |
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| Can interventional drainage of lymph from the thoracic duct be used in the therapeutic management of heart failure (shunting or externalizing)? |
| What are the implications of molecular and structural differences within the lymphatic vasculature on congestion in heart failure? |
| Are there different degrees of these differences among patients? Would that explain different manifestations of heart failure in different patients with the same degree of volume overload (eg, more ascites than pedal edema in some patients, whereas others have no ascites)? |
| What is the role of inflammation in lymphatic disturbance in heart failure and the potential role of anti-inflammatory agents? |
| What is the role of pro-lymphangiogenic factors (eg, vascular endothelial growth factor C and D) in counteracting cardiac remodeling in various conditions, such as ischemia, hypertension, and aging? |
| Are patients with congenital lymphatic disorders at increased risk of heart failure? |
| What is the role of genetics as a driver of heart failure through lymphatic disruption? |

bilateral inguinal lymph nodes using 25-gauge spinal needles under ultrasound guidance followed by injection of oil-based contrast under fluoroscopic guidance (50). Dynamic contrast enhanced magnetic resonance lymphangiography is an evolving imaging technique that involves ultrasound-guided injection of gadolinium-based contrast into the inguinal lymph nodes followed by imaging of the chest and abdomen using a 3-dimensional imaging protocol with high spatial resolution (51) (Figure 3).

THORACIC DUCT CANNULATION. Thoracic duct cannulation has important diagnostic and therapeutic values (49). Diagnostically, thoracic duct cannulation can be used to calculate the lymph flow rate and pressure within the thoracic duct, characterize the composition of lymph in the thoracic duct, and aid in the differential diagnosis of different lymphatic-related disorder (49). Thoracic duct cannulation also has several potential therapeutic uses, such as management of ascites in hepatic cirrhosis, limiting edema in acute pancreatitis, and possibly with control of fluid volume in HF (49).

Techniques for accessing the thoracic duct have evolved over the years. Historically, access to the thoracic duct is achieved through surgical cannulation of the cervical portion of the duct under local anesthesia using a polyethylene or silastic catheter (48,49,52). The catheter can be left in the thoracic duct for many days as needed. It can then be removed at bedside with the application of pressure dressing (48,49,52). This technique is currently not in clinical use.

Recently, interventional radiologists have accessed the cervical thoracic duct using a direct percutaneous access (53,54). Following lymphangiography, fluoroscopic images of the cervical portion of the thoracic duct (left neck area) typically show opacification of the thoracic duct. Using a combination of ultrasound

and fluoroscopic guidance, a needle can be advanced into the cervical portion of the thoracic duct followed by a guidewire exchanged for a microcatheter, which can be left in place for several days to drain lymph as needed (53-55). Interventional radiologists are accustomed to use this technique for the management of thoracic duct leakage (eg, thoracic duct embolization) with the point of entry most frequently being the cisterna chyli (56) (Figure 4). Thoracic duct cannulation is an overall safe procedure with a complication rate of 3% (eg, leg edema) (56).

TARGETING THE LYMPHATIC SYSTEM IN THE MANAGEMENT OF HF

Tissue and organ congestion in HF is not merely attributable to the central venous congestion, but integrally involves the lymphatic system as well. Management of acute decompensated HF focuses initially on venous decongestion via diuretic therapy and venodilation/vasodilation. Many therapies targeting vasodilation, augmented diuresis, or ultrafiltration, in the acute phase of the disease, have failed to demonstrate improved outcomes compared with the current standard of care. Diuretic resistance is a common barrier to achieving euvolemia and increases time to both symptom resolution and hemodynamic stability (57). Notably, despite best efforts, clinical outcomes in hospitalized HF patients remain poor, and readmission rates for HF consistently top any other diagnosis in the United States. Thus, we propose that interventions directly targeting decongestion of the lymphatic system could provide a novel pathway to relieve tissue congestion and improve target organ function.

To date, a number of studies have investigated the feasibility and effectiveness of lymphatic drainage in HF. Cole et al. (58) constructed a lymphovenous anastomosis via thoracic duct-to-pulmonary vein shunt in dogs with right-sided HF. The shunt resulted in reduced systemic venous pressure, increased urinary sodium excretion within a few hours, and significant reduction in ascites in 77% of the dogs. In a sheep model (59), pulmonary edema was induced by maintaining a left atrial pressure of 35 mm Hg. Sheep with thoracic duct drainage had significantly less pulmonary edema and smaller pleural effusion compared with sheep without thoracic duct drainage.

Human studies using a therapeutic approach to lymph drainage are summarized in the following text:

1. In a study in 1963, in patients with intractable HF who failed to improve with medical therapy,

cervical thoracic duct cannulation resulted in a significant drop in venous pressures and improvement in symptoms and signs of HF (ie, distended neck veins, peripheral edema, ascites, dyspnea, and orthopnea) (48). Thoracic duct cannulation in these patients also provided important diagnostic values about thoracic duct changes in patients with HF; the diameter of the duct in these patients was 2-4 times the normal diameter of about 2 mm, and the lymph flow rate was 4-12 times the normal rate. After resolution of signs of HF in these patients, the investigators reduced the flow rate to the normal rate (1 mL/min) for several hours; this resulted in reappearance of signs of HF in these patients (48).

2. In 1969, a second study (52) tested cervical thoracic duct cannulation in patients with advanced HF. Thoracic duct drainage reduced symptom burden and signs of volume overload, decreased the CVP from a mean of 32 to 14 cm H₂O, and increased the urinary output (52). The diameter of the thoracic duct in all of these patients was enlarged up to 6 times the normal diameter.

3. Although lymphovenous anastomosis has not been studied in humans as a method to manage HF, a study from 1975 used a thoracic duct-to-internal jugular vein shunt to treat patients with cirrhosis and intractable ascites. In all of the patients, the thoracic duct was dilated an average of 3 times the normal diameter and demonstrated an increased intraductal pressure. Almost one-half of the patients had improvement in their ascites following the procedure, and 25% of the patients had significant reduction in the frequency of therapeutic paracentesis (60).

CONCLUSIONS

The lymphatic system plays a central role in volume management, and dysregulation of the lymphatic system underlies most of the classical signs and symptoms in HF, such as lower extremity and pulmonary edema and cardiorenal syndrome. Therefore, we propose that targeting the lymphatic system in HF can potentially provide a novel pathway to decongest tissue and improve target organ function. We provide preclinical and clinical data to support the feasibility of targeting the lymphatic system in HF through a number of potential approaches. Novel device-based interventions are under active investigation to enhance thoracic duct drainage in acute decompensated HF (Table).

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Biomedical. Dr Patel has received research grants from AstraZeneca, Bayer, Janssen, Procyron, and Heartflow; and is on the advisory board for Bayer, Janssen, Mytonomy, and Procyron. NXT Biomedical has applied for a patent related to therapy targeting the lymphatic system. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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